

Art Unit: 1652

EAST:

BRS L1 54995 polymerase USPAT 2009/03/12 13:59
BRS L2 4618 polymerase.clm. USPAT 2009/03/12 13:59
BRS L3 2455 12 and (mutant or variant) USPAT 2009/03/12 14:00
BRS L4 1964 12 and ("410" or "542" or "543" or "593" or "595" or "385"
or "387" or "388") USPAT 2009/03/12 14:01
BRS L5 1285 13 and 14 USPAT 2009/03/12 14:01
BRS L6 377 15 and (pfu or pyrococcus) USPAT 2009/03/12 14:06
BRS L7 51 15 and (pfu or pyrococcus).clm. USPAT 2009/03/12 14:06
BRS L8 0 17 and ("410" or "542" or "543" or "593" or "595" or "385"
or "387" or "388").clm.USPAT 2009/03/12 14:09
BRS L9 23 12 and ("410" or "542" or "543" or "593" or "595" or "385"
or "387" or "388").clm.USPAT 2009/03/12 14:09
BRS L11 28 reduced adj polymerase USPAT 2009/03/12 14:32
BRS L12 1 110 and 111 USPAT 2009/03/12 14:32
BRS L10 10 less adj polymerase USPAT 2009/03/12 14:32

Separate EAST Search:

BRS L1 313 reduced adj polymerization USPAT 2009/03/12 14:41
BRS L2 5 (reduced adj polymerization).clm. USPAT 2009/03/12 14:42
BRS L3 29 11 and polymerase USPAT 2009/03/12 14:42
BRS L4 29 13 and (mutant or variant) USPAT 2009/03/12 14:45
BRS L5 25 14 and polymerase.clm. USPAT 2009/03/12 14:46

US-PAT-NO: 5541311

DOCUMENT-IDENTIFIER: US 5541311 A

See image for Certificate of Correction

TITLE: Nucleic acid encoding synthesis-deficient thermostable
DNA polymerase

DATE-ISSUED: July 30, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE
COUNTRY			
Dahlberg; James E.	Madison	WI	N/A
N/A			
Lyamichev; Victor I.	Madison	WI	N/A
N/A			
Brow; Mary Ann D.	Madison	WI	N/A
N/A			

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE
COUNTRY TYPE CODE			
Third Wave	Monrovia	CA	N/A N/A
02			
Technologies, Inc.			

APPL-NO: 08/073384

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DATE FILED: June 4, 1993

PARENT-CASE:

This is a continuation-in-part of application Ser. No. 07/986,330, filed Dec. 12, 1992, now abandoned.

US 7,452,665

to A kit for the synthesis of a polynucleotide, said kit comprising A mixture comprising: (a) a first DNA **polymerase** wherein said first **polymerase** possesses 3'-5' exonuclease activity selected from the group consisting of Archaeobacterial DNA polymerases, and (b) a second DNA **polymerase** wherein said second **polymerase** lacks 3'-5' exonuclease activity selected from the group consisting of thermostable DNA polymerases lacking 3'-5' exonuclease activity; wherein the ratio of DNA **polymerase** activity of the first DNA **polymerase** to the DNA **polymerase** activity of the second DNA **polymerase** is from about 1:100 up to about 1:600.

2. A kit according to claim 1, wherein said *Thermus aquaticus* DNA **polymerase** is selected from the group consisting of wild-type *Thermus aquaticus* DNA **polymerase** and N-terminal deleted forms of the same enzyme.

3. A kit according to claim 1, wherein said first DNA **polymerase** comprises *Pyrococcus furiosus* DNA **polymerase**.

4. A kit according to claim 1, wherein said second DNA **polymerase** comprises *Thermus aquaticus* DNA **polymerase**.

5. A kit according to claim 2, wherein said *Thermus aquaticus* DNA **polymerase** comprises KlenTaq-278 DNA **polymerase**.

STN: (FILE 'HOME' ENTERED AT 14:57:59 ON 12 MAR 2009)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, JAPIO, BIOTECHNO' ENTERED AT
14:59:22 ON 12 MAR 2009

L1 1413080 S POLYMERASE

L2 11 S L1 AND REDUCED POLYMERIZATION

L3 595 S L1 AND REDUCED ACTIVITY

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L4 4 DUP REM L2 (7 DUPLICATES REMOVED)

L5 4144 S L1 AND (410 OR 542 OR 543 OR 593 OR 595 OR 385 OR 387 OR
388)

L6 473 S L5 AND (MUTANT OR VARIANT)

L7 0 S L6 AND (Y410 OR T542 OR D543 OR K593 OR Y595 OR Y385 OR
G387L8 27 S L1 AND (Y410 OR T542 OR D543 OR K593 OR Y595 OR Y385 OR
G387

L9 8 DUP REM L8 (19 DUPLICATES REMOVED)

L9 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2003:757196 CAPLUS

DN 139:287250

TI High fidelity DNA polymerase compositions with improved proof
reading activity containing mutant polymerase with mutations in
polymerase domain or partitioning domain and uses therefor

IN Hogrefe, Holly; Borns, Michael; Sorge, Joseph

PA USA

SO U.S. Pat. Appl. Publ., 127 pp., Cont.-in-part of U.S. Ser. No. 79,241.
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20030180741	A1	20030925	US 2002-208508	20020730
	US 20030143577	A1	20030731	US 2002-227110	20020823
	CA 2471473	A1	20030724	CA 2002-2471473	20021217
	WO 2003060144	A2	20030724	WO 2002-US40423	20021217
	WO 2003060144	A3	20031023		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2002360638	A1	20030730	AU 2002-360638	20021217
	EP 1463808	A2	20041006	EP 2002-795911	20021217
	EP 1463808	B1	20090211		
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
	JP 2005514072	T	20050519	JP 2003-560226	20021217

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AT 422537 T 20090215 AT 2002-795911 20021217
PRAI US 2001-35091 A2 20011221
US 2002-79241 A2 20020220
US 2002-208508 A2 20020730
US 2002-227110 A 20020823
WO 2002-US40423 W 20021217

AB The subject invention relates to compns. comprising an enzyme mixt. which comprises a first enzyme and a second enzyme, where the first enzyme comprises a DNA polymn. activity and the second enzyme comprises an 3'-5' exonuclease activity and a reduced DNA polymn. activity. The first enzyme is a DNA polymerase with or without 3'.fwdarw.5'-exonuclease activity, and preferably Pfu DNA polymerase from *Pyrococcus furiosus* or Taq DNA polymerase from *Thermus aquaticus* or reverse transcriptase, and the second enzyme may be a mutant Pfu DNA polymerase with reduced DNA polymn. activity and concomitant 3'.fwdarw.5'-exonuclease activity. Other mutant DNA polymerase can be derived from the group consisting of: Taq DNA polymerase, Tth DNA polymerase, ULTma DNA polymerase, Tli DNA polymerase, Pfu DNA polymerase, KOD DNA polymerase, JDF-3 DNA polymerase, Tgo DNA polymerase, PGB-D DNA polymerase and DP1/ DP2 DNA polymerase. Specifically, disclosed are the protein and gene sequences for the above DNA polymerase mutants with mutations in their partitioning domains or polymerase domains. The Pfu mutants tested to show <10 % DNA polymerase activity and at least 10 % exonuclease activity, include the partitioning domain mutants: Y385[Q|S|N|L|H], G387SP, and G388P and the polymerase domain mutants: D405E, T542P, D543G, and K593T. The recombinant Pfu G387P mutants (with or without His6-Tag) is purified and added to Pfu or Taq DNA polymerase to form various blends (different range of mixing ratios) to improve the amplification fidelity and efficiencies. The invention also relates to the above compns. in kit format and methods for high fidelity DNA synthesis using the subject compns. of the invention

DETAILED ACTION

Applicant's amendment of claims 1, 12, 36, 40, 44, 48, 49 and 50 in the paper of 12/19/2008, is acknowledged. Applicants' arguments filed on 12/19/2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office

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actions are hereby withdrawn. Claims 1, 3, 10-12, 14, 20, 22-24, 26, and 30-51 are still at issue and are present for examination.

Claims 23, 24, 26 and 30-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 10, 11, 12, 14, 20, 22 and 36-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

???????

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 48-51. In response to the rejection, applicants have amended claims 48, 49 and 50 and traverse the rejection as it applies to the newly amended claims.

Applicants continue to traverse the written description rejection together with the rejection based upon a lack of scope of enablement together on the basis that the Office has misinterpreted the claim language. Applicants submit that independent claims 48-50 recite the phrase "at least one amino acid position selected from the group consisting of" followed by a specific recitation of various amino acids/positions within an enzyme. Applicants continue to submit that this claim language is standard "Markush"-type language used in U.S. patent practice, and specifically approved by the MPEP (see MPEP § 2173.05(h)). As stated in the MPEP, claiming using a "Markush" group is a manner of claiming "a genus expressed as a group consisting of certain specified materials." Within the context of the present claims, the genus is a mutated enzyme specified as having at least one of a well-defined number of specific mutations. Applicants submit that the present claim language, and in particular the phrase "at least one", indicates to those of skill in the art that the genus described by the "Markush" group is not limited to enzymes with single mutations, but to enzymes having one or multiple mutations selected from the recited group. The claims clearly indicate which mutation or mutations are within the group from which mutations may be selected, and the claim language cited by the Office does not relate to mutations outside of those specifically recited in the "Markush" group.

Applicants further submit that in contrast to the clear language and meaning of the claims, in setting forth the rejection, the Office has parsed the phrase "at least one amino acid position selected from the group consisting of" into two separate and distinct phrases: "at least one" and "amino acid position selected from the group consisting of." Specifically, the Office interprets the phrase "at least" in the context of claims 48-50 "as allowing additional mutations outside the referenced positions, such that applicants have not adequately described [or enabled] this genus."

Applicants submit that doing so is improper because it is inconsistent with the clear meaning of the claim language. Applicants submit that it is also inconsistent with controlling case law from the Federal Circuit.

Applicants cite the "Meeting Held to Promote Uniform Practice In Chemical Divisions," 28 J. Pat. & Trademark Off. Soc'y 849, 852 (1946), the Federal Circuit recognized examples of qualifying language in Markush groups that was approved by the USPTO, including "and mixtures thereof" and "at least one member of the group." Id. Thus, as acknowledged by the Federal Circuit, it has long been common practice to use expressions like "at least one" in the context of Markush language to indicate that the claim covers one or more members of the recited Markush group. Applicants submit that therefore, in our case, the language 'at least one' and 'chosen from the group consisting of' in our judgment modifies the word substituent, allowing the patentee to select more than one substituent from among the Markush group. Thus, Applicants submit that the Office's interpretation of the Markush language at issue is incorrect and its position on written description and enablement moot. Rather, the correct claim

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interpretation must be that discussed above, which is fully consistent with U.S. law, U.S. patent regulations, and USPTO examination guidelines.

Applicant's amendment and complete argument is acknowledged and has been carefully considered, however, is found non-persuasive for claims 48-51 for the reasons previously made of record and repeated herein. The basis for this rejection is applicant's recitation in these claims to "Pfu DNA polymerase, except that it is mutated in at least one amino acid position...". Applicants continued argument that this language is standard Markush"-type language is not found persuasive. Applicant's attention is directed to that portion of that section of the MPEP to which applicants refer, which states that :

Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). *Ex parte Markush* sanctions claiming a genus expressed as a group consisting of certain specified materials.

As previously stated applicants use of the phrase "Pfu DNA polymerase, except that it is mutated in at least one amino acid position..." is the basis of the current rejection. It is the offices continued position that the office is not parsing the indicated phrase, but merely interpreting as broadly as is reasonable, given the art and applicants specification.

As has been previously stated, this recited limitation of the second enzyme of the claimed kits removes the necessary structural limitations that are required to adequately

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describe the second enzyme which started out prior to any mutation as Pfu DNA polymerase, as identified at Accession No. Applicant's attention continues to be directed to the wording "at least", as it compares to the wording of applicants claim 1. Such language of the instant claim is interpreted as allowing additional mutations outside the referenced positions, such that applicants have not adequately described this genus.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme mixture comprising a first and second enzyme, wherein said first enzyme is a DNA polymerase or reverse transcriptase and said second enzyme is a Pfu DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 19 with a mutation selected from the group consisting of Y410, T542, D543, K593, Y595, Y385, G387 and G388, does not reasonably provide enablement for an enzyme mixture comprising a first and second enzyme, wherein said first enzyme is a DNA polymerase or reverse transcriptase and said second enzyme is a mutant Pfu DNA polymerase except that it is mutated in at least one amino acid position selected from the group consisting of: Y410, T542, D543, K593, Y595, Y385, G387 and G388. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 48-51. In response to the rejection, applicants have amended claims 48, 49 and 50 and traverse the rejection as it applies to the newly amended claims.

As pointed out above, applicants traverse the rejection based upon a lack of scope of enablement together with the above rejection under written description on the basis that the Office has misinterpreted the claim language. Applicants continue to submit that independent claims 48-50 recite the phrase "at least one amino acid position selected from the group consisting of" followed by a specific recitation of various amino acids/positions within an enzyme. Applicants continue to submit that this claim language is standard "Markush"-type language used in U.S. patent practice, and specifically approved by the MPEP (see MPEP § 2173.05(h)). As stated in the MPEP, claiming using a "Markush" group is a manner of claiming "a genus expressed as a group consisting of certain specified materials." Within the context of the present claims, the genus is a mutated enzyme specified as having at least one of a well-defined number of specific mutations. Applicants continue to submit that the present claim language, and in particular the phrase "at least one", indicates to those of skill in the art that the genus described by the "Markush" group is not limited to enzymes with single mutations, but to enzymes having one or multiple mutations selected from the recited group. The claims clearly indicate which mutation or mutations are within the group from which mutations may be selected, and the claim language cited by the

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Office does not relate to mutations outside of those specifically recited in the "Markush" group.

Thus, Applicants submit the Office's interpretation of the language of claims 48-51 is incorrect, and its position on written description and enablement moot. For at least this reason, Applicants request that the Office reconsider and withdraw the rejection of claims 48-51 under 35 U.S.C. § 112, first paragraph.

As stated above, applicant's amendment and complete argument is acknowledged and has been carefully considered, however, is found non-persuasive for claims 48-51 for the reasons previously made of record and repeated herein. The basis for this rejection continues to be that applicant's recitation in these claims to "Pfu DNA polymerase, except that it is mutated in at least one amino acid position...". Applicants argument that this language is standard Markush"-type language is not found persuasive. Applicant's attention is directed to that portion of that section of the MPEP to which applicants refer, which states that :

Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). *Ex parte Markush* sanctions claiming a genus expressed as a group consisting of certain specified materials.

As previously stated applicants use of the phrase "Pfu DNA polymerase, except that it is mutated in at least one amino acid position..." is the basis of the current rejection. It is the office's continued position that the office is not parsing the indicated

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phrase, but merely interpreting as broadly as is reasonable, given the art and applicants specification.

As has been previously stated and repeated above, this recited limitation of the second enzyme of the claimed kits removes the necessary structural limitations that are required to sufficiently enable the second enzyme which started out prior to any mutation as Pfu DNA polymerase. Applicant's attention continues to be directed to the wording "at least", as it compares to the wording of applicants claim 1. Such language of the instant claim is interpreted as allowing additional mutations outside the referenced positions, such that applicants have not sufficiently enabled this genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any enzyme mixture comprising any Pfu DNA polymerase with at least the specified mutations. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

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and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 10-12, 14, 20, 22 and 36-51 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 64-70, 75-87 of copending Application No. 10/079,241. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed enzyme mixtures of the instant application, comprising a first enzyme and a second enzyme wherein said first enzyme comprises a DNA polymerization activity and said second enzyme is a mutant Pfu DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon are anticipated by and thus obvious over the corresponding claims of copending Application No. 10/079,241, drawn to a enzyme mixture comprising a first enzyme and a second enzyme wherein said first enzyme is an Archaeal DNA polymerase and said second enzyme is a mutant Archaeal DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410,

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T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant acknowledgment of this provisional rejection is acknowledged, as well as applicant's statement of their intent of filing a terminal disclaimer as a means of overcoming the rejection at the time at which the claims are found otherwise allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rg
3/12/2009

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652